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Letter

$B(C_6F_5)_3$-Catalyzed Direct C3 Alkylation of Indoles and Oxindoles

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Cite This: *ACS Catal.* 2020, 10, 4835−4840

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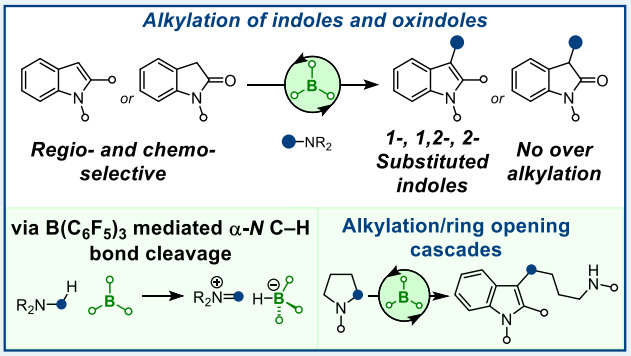
ABSTRACT: The direct C3 alkylation of indoles and oxindoles is a challenging transformation, and only a few direct methods exist. Utilizing the underexplored ability of triaryl boranes to mediate the heterolytic cleavage of α-nitrogen C−H bonds in amines, we have developed a catalytic approach for the direct C3 alkylation of a wide range of indoles and oxindoles using amine-based alkylating agents. We also employed this borane-catalyzed strategy in an alkylation-ring opening cascade.



KEYWORDS: *catalysis, boranes, N-heterocycles, alkylation, indoles, oxindoles*

Indoles and oxindoles are prevalent motifs in biologically active molecules.[1] Classic indole syntheses involve ring construction.[2] Another approach involves the functionalization of the readily accessible heterocycle core; yet, the direct and selective C3 alkylation of indoles and oxindoles is a surprisingly challenging transformation as the reaction with simple alkyl halides is often not synthetically useful.[2,3] For example, with methyl iodide, 1,2-dimethylindole and 1-methylindole are unreactive,[4] 2-methylindole results in mixtures of *N*- and *C*-methylation,[5] and oxindoles undergo dialkylation at C3.[3] The installation of a methyl group is a worthwhile endeavor, considering the interest of medicinal chemists in the "magic methyl effect";[6] yet only a few methods exist for the direct C3 methylation of indoles and oxindoles (Scheme 1a). Direct C3 methylation is possible with CO_2/H_2 and a ruthenium catalyst (e.g., for 1,2-dimethylindole and 2-methylindole),[7] and with borrowing hydrogen methods with methanol (e.g., for 2-methylindole[8] and 1-phenyl oxindole).[8a,9] The direct methylation of 1-methylindole is currently unknown.[4]

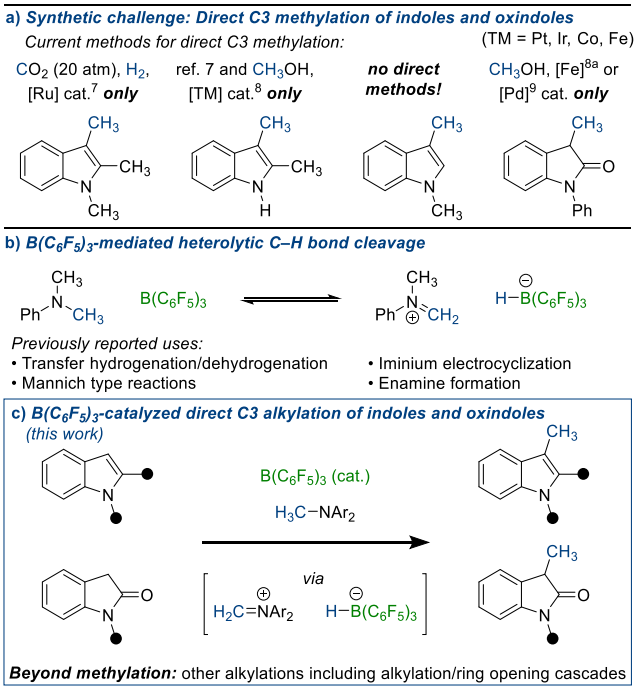
Because of their intrinsic Lewis acidity, borane catalysts have found numerous applications in synthesis and are traditionally used to activate polarized bonds.[10] Triaryl boranes can also activate unpolarized bonds, such as H−H[11] and Si−H bonds.[12] In a similar vein, we considered if boranes could also be used to cleave $C(sp^3)$−H bonds heterolytically[13] and unveil new approaches to challenging transformations. Related to this, we were intrigued by a report by Santini that described the heterolytic cleavage of an α-nitrogen $C(sp^3)$−H bond during the stoichiometric reaction of dimethyl aniline and $B(C_6F_5)_3$ to form an iminium borohydride ion pair (Scheme 1b).[14] $B(C_6F_5)_3$-mediated α-N $C(sp^3)$−H bond cleavage[15] was unrecognized as a synthetic strategy for almost a decade until Stephan and co-workers reported its use in the transfer hydrogenation of imines.[16] Subsequently, Grimme and Paradies,[17a] Kanai,[17b] and Zhang[17c] disclosed methods for the dehydrogenation of *N*-heterocycles. A major breakthrough came when Erker reported the use of this unusual reactivity in C−C bond-forming reactions where stoichiometric $B(C_6F_5)_3$ was used to generate iminium ions for Mannich-type processes.[18] Wasa greatly advanced the strategy by reporting the catalytic use of $B(C_6F_5)_3$ in an asymmetric Mannich process.[19] The iminium ions generated have also been used in electrocyclizations,[20] and in the β-functionalization of amines.[21,22] However, the use of this reactivity in catalytic C−C bond-forming reactions remains rare.[19,20] Inspired by these reports and borrowing hydrogen alkylation reactions,[23] we have applied this underutilized reactivity in challenging alkylation processes.

Here, we have developed a new strategy for the direct C3 methylation of indoles and oxindoles (Scheme 1c). The process utilizes a $B(C_6F_5)_3$-mediated α-N $C(sp^3)$−H bond cleavage events to activate readily available amine-based alkylating agents. Using this borane-catalyzed method, common undesired reactions, such as the *N*-methylation of

Received: March 9, 2020
Revised: April 2, 2020
Published: April 9, 2020

https://dx.doi.org/10.1021/acscatal.0c01141
ACS Catal. 2020, 10, 4835−4840

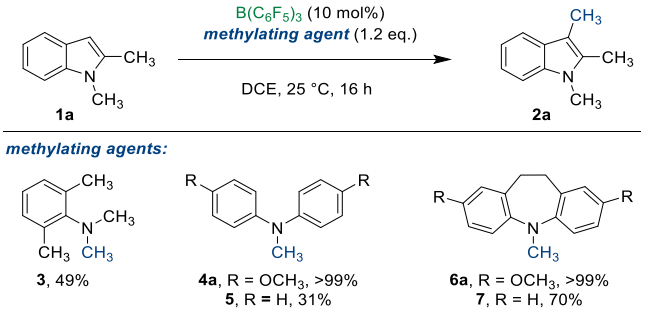
Scheme 1. $B(C_6F_5)_3$-Catalyzed α-N $C(sp^3)$–H Bond Cleavage Used in the Methylation of Indoles and Oxindoles



indoles, the formation of 3,3′-bisindolylmethanes, and the dialkylation of oxindoles, are not observed. In addition, the substrate scope is broad and encompasses 1-, 2-, and 1,2-substituted indoles, as well as other challenging alkylations, including a novel alkylation-ring opening cascade.

We began by investigating various aniline derivatives as methylating agents in the borane-catalyzed methylation of 1,2-dimethyl indole (**1a**) (Scheme 2). Generally, we discovered

Scheme 2. $B(C_6F_5)_3$-Catalyzed Methylation of Indole 1a with Various Alkylating Agents[a]



[a]Reactions were performed using 0.2 mmol of **1a**. Yields were determined after ^{1}H NMR spectrum analysis of the crude reaction mixture with an internal standard.

that a variety of aryl and diaryl amines were effective in methylating **1a** using $B(C_6F_5)_3$ (10 mol %).[24] Electron-rich diaryl methyl amines, such as **4a** and **6a**, were determined to be optimal and allowed the formation of **2a** in quantitative yields at ambient temperature.

We surveyed the scope of the $B(C_6F_5)_3$-catalyzed methylation of various 1,2-, 1-, and 2-substituted indoles and oxindoles and found that the reaction broadly tolerated a range of functional groups and substitution patterns (Scheme 3). Notably, the direct methylation of 1-methylindole (**1f**), which is a transformation that was previously absent from the literature,[4] was successfully accomplished in high isolated yield (**2f**, 75%) using the $B(C_6F_5)_3$-catalyzed approach with methylating agent **6a**.[25] 2-Substituted indoles (i.e., NH indoles, cf. **2l**–**2s**) were efficiently methylated when 2,2,6,6-tetramethylpiperidine (TMP, 10 mol %) was used with alkylating agent **6a** and $B(C_6F_5)_3$ (10 mol %).[26] Importantly, *N*-methylation was not observed with NH-bearing indoles. In contrast, *N*-alkylation, or mixtures of *N*- and *C*-alkylation, typically result when NH indoles are treated with methyl iodide under basic conditions.[5] The successful reaction of 1- (cf. **2f**–**2k**) and 2-substituted indoles (cf. **2l**–**2s**) was surprising, given that $B(C_6F_5)_3$ has been reported to react readily with these classes of heterocycle to produce zwitterionic species.[27] 3,3′-Bisindolylmethanes, which are a common product formed in the reaction of formaldehyde or iminium electrophiles with indoles, were not observed.[28]

Oxindoles (**8a**–**8q**) were successfully employed in the $B(C_6F_5)_3$-catalyzed methylation to give products **9a**–**9q**. In this class of heterocycle, 1,2,2,6,6-pentamethylpiperidine (PMP, **13**) was used as the alkylating agent and higher temperatures were required. Crucially, C3 dimethylation was not observed. Therefore, the borane-catalyzed process complements traditional alkylating agents: C3 dialkylation typically occurs when oxindoles are treated with methyl iodide under basic conditions.[3]

The methylation of 6-methylindole (cf. **2n**) and unsubstituted oxindole (cf. **9n**) occurred in low yield, presumably because of competitive coordination of N or O to the $B(C_6F_5)_3$ catalyst. Otherwise, across the different classes of substrates, the process tolerated a range of functional groups and substituents, such as OCH_3 (**2c**, **2s**, **9i**, **9k**), F (**2o**, **9d**), Cl (**2d**, **2p**, **9e**), Br (**2q**, **9f**), CF_3 (**9m**), NO_2 (**2e**, **9j**), CO_2Me (**9c**), and other carbonyl derivatives (**9o**, **9p**), which contrasts the dogma sometimes associated with $B(C_6F_5)_3$-mediated processes.[29] We also performed the $B(C_6F_5)_3$-catalyzed methylation of 1,2-dimethylindole (**1a**) on a preparative scale, producing 1.3 g of 1,2,3-trimethylindole (**2a**) in 83% yield.[30]

In addition, we briefly explored other challenging alkylation reactions using the $B(C_6F_5)_3$-catalyzed method and discovered that 1,2-dimethylindole (**1a**) was successfully ethylated (**10a**), decylated (**11a**) and benzylated (**12a**), at C3 using the ethyl- (**6b**), decyl- (**6c**), or benzyl- (**4b**)[31] diaryl amines, respectively.[32]

The borane catalyst, $B(C_6F_5)_3$, is a commercially available white powder that forms a water adduct, $H_2O{\cdot}B(C_6F_5)_3$, when exposed to moisture in air and is therefore routinely handled in an inert atmosphere.[33] Inspired by related methods,[34] we developed a procedure where $B(C_6F_5)_3$ can be used as received from the supplier and weighed in air on the open bench, and the reaction performed using standard Schlenk line techniques (Scheme 4). Thus, $H_2O{\cdot}B(C_6F_5)_3$ (10 mol %) was dissolved in the desired solvents (as received from the supplier) and treated with triethyl silane (20 mol %). The resultant solution contains active $B(C_6F_5)_3$ and $O(SiEt_3)_2$ that can be used directly in the alkylation of indoles and oxindoles to provide methylated indoles (**2a**, **2f**, and **2l**), benzylated indole (**12a**), and methylated oxindole (**9a**)[35] in good yields. Therefore, this shows that access to specialized equipment (such as a dry glovebox), a separate purification of commercially available

https://dx.doi.org/10.1021/acscatal.0c01141
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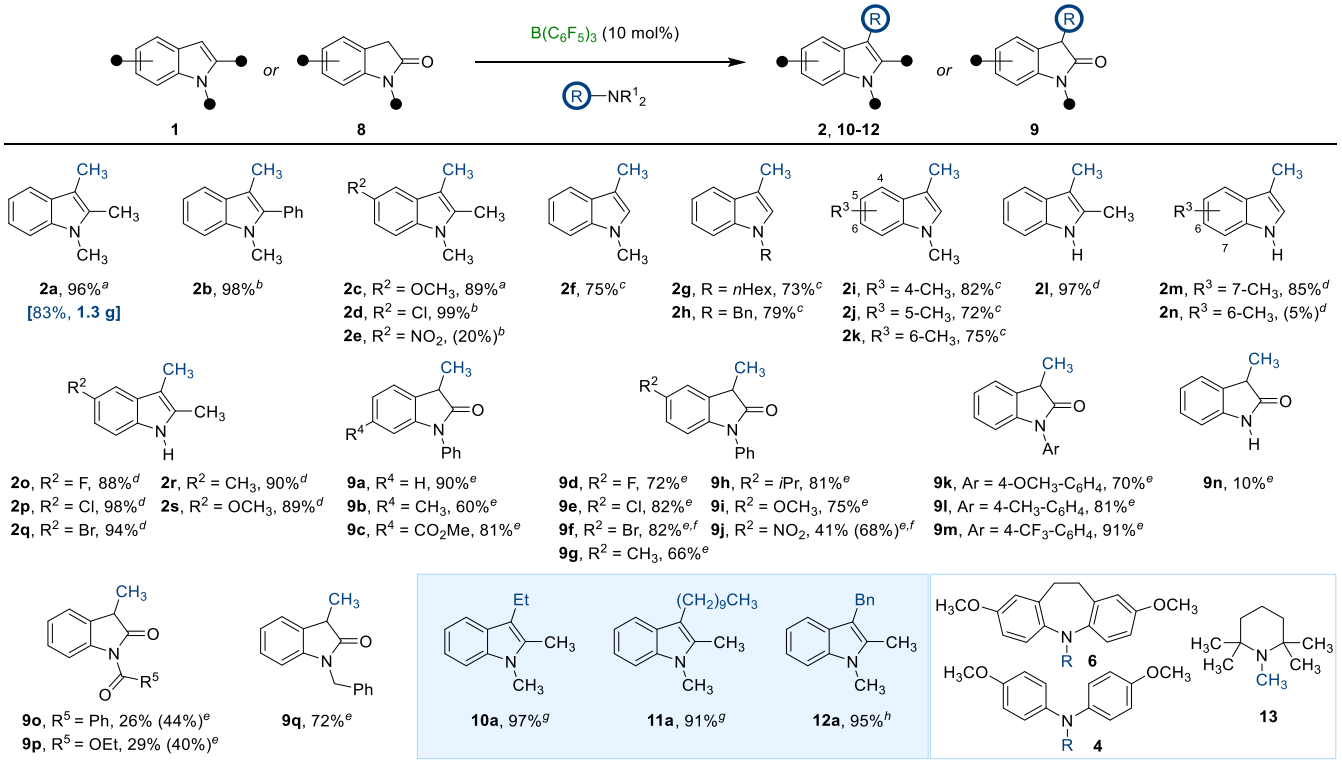
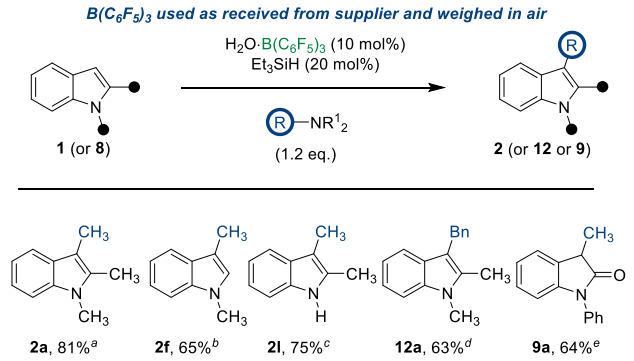
Scheme 3. Substrate Scope in the $B(C_6F_5)_3$-Catalyzed Alkylation of Indoles and Oxindoles*



*Reactions were performed using 0.5 mmol of **1** or **8** except conditions g and h, where 0.2 mmol of **1a** was used. Yields are isolated. Yields in parentheses determined after ^{1}H NMR spectrum analysis of the crude reaction mixture with an internal standard. [a]$B(C_6F_5)$ (10 mol %), **6a** (R = CH_3, 1.2 equiv), 25 °C, DCE, 16 h. [b]$B(C_6F_5)_3$ (10 mol %), **6a** (R = CH_3, 1.2 equiv), 95 °C, DCE, 16 h. [c]$B(C_6F_5)_3$ (20 mol %), **6a** (R = CH_3, 1.2 equiv), 95 °C, DCE, 8 h. [d]$B(C_6F_5)_3$ (10 mol %), **6a** (R = CH_3, 1.2 equiv), TMP (10 mol %), 110 °C, toluene, 16 h. [e]$B(C_6F_5)_3$ (10 mol %), **13** (PMP, 2 equiv), 150 °C, xylenes, 16 h. [f]Combined yield of tautomers. [g]$B(C_6F_5)_3$ (10 mol %), **6b** (R = Et) or **6c** (R = $(CH_2)_9CH_3$) (1.2 equiv), 95 °C, DCE, 24 h. [h]$B(C_6F_5)_3$ (20 mol %), **4b** (R = Bn, 2 equiv), 150 °C, xylenes, 24 h.

Scheme 4. Use of $H_2O{\cdot}B(C_6F_5)_3$ in the Borane-Catalyzed Alkylation of Indoles and Oxindoles

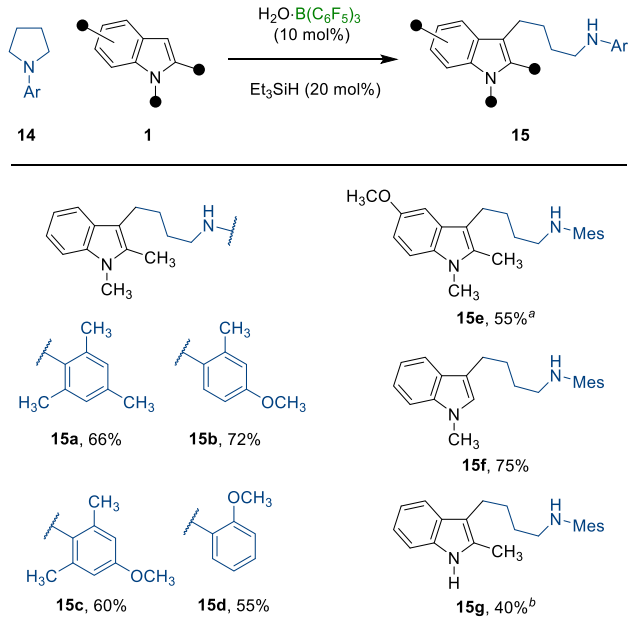


[a]**6a**, 25 °C, DCE, 16 h. [b]**6a**, $B(C_6F_5)_3$ (20 mol %), Et_3SiH (40 mol %), 95 °C, DCE, 8 h. [c]**6a**, TMP (10 mol %), 110 °C, toluene, 16 h. [d]**4b**, 150 °C, *p*-xylene, 24 h. [e]PMP (**13**) (2 equiv), 150 °C, *p*-xylene, 16 h.

$B(C_6F_5)_3$, and rigorously anhydrous solvent is not required in the $B(C_6F_5)_3$-catalyzed alkylation.

Beyond methylation and alkylation, we also explored the $B(C_6F_5)_3$-catalyzed alkylation strategy in a novel alkylation-ring opening cascade process for the generation of functionalized indoles **15** (Scheme 5). Product **15** contains a 4-(3-indolyl)butylamine motif that is found in several serotonergic/dopaminergic drug molecules, such as vilazodone, roxindole, siramesine, and carmoxirole.[36] Upon reaction of *N*-aryl

Scheme 5. $B(C_6F_5)_3$-Catalyzed Alkylation-Ring Opening Cascade*



*Standard conditions: $H_2O{\cdot}B(C_6F_5)_3$ (10 mol %), Et_3SiH (20 mol %), **14** (1 equiv), **1** (2.2 equiv), 1,2-$Cl_2C_6H_4$, 110 °C, 20–24 h. [a]DCE, 85 °C. [b]Toluene.

https://dx.doi.org/10.1021/acscatal.0c01141
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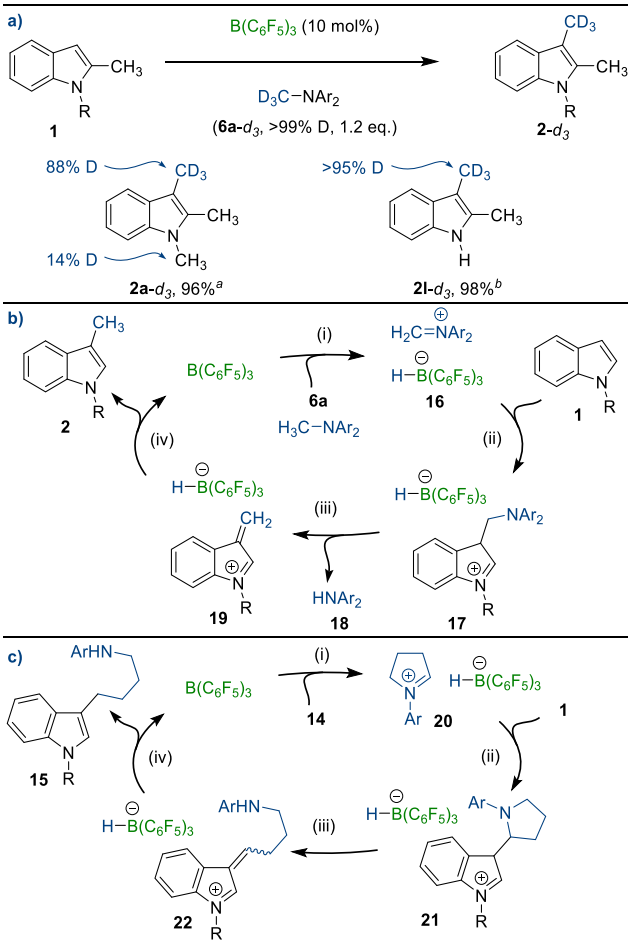
pyrrolidines **14**,[37] indoles **1** and $B(C_6F_5)_3$ catalyst, a variety of 4-(3-indolyl)butylamines **15** were formed in good yields.[38]

In order to probe the mechanism and provide direct access to deuterated methyl groups at C3 of indoles, we used deuterated methylating agent **6a**-d_3 in the $B(C_6F_5)_3$-catalyzed methylation of indoles **1a** and **1l** under previously optimized conditions (Scheme 6a). Deuterated C3 methylindoles **2a**-d_3 and **2l**-d_3 were formed in high yield in both cases.[39]

Scheme 6. Mechanistic Studies and Proposed Catalytic Cycle*



*Yields are isolated and %D incorporation was determined after ^{1}H NMR spectrum analysis of the purified compounds. [a]DCE, 25 °C, 16 h. [b]TMP (10 mol %), toluene, 110 °C, 16 h.

Based on these results and literature precedent, we propose the following catalytic cycle for the $B(C_6F_5)_3$-catalyzed alkylation of indoles and oxindoles (Scheme 6b). The borane-catalyst mediates heterolytic cleavage, via hydride abstraction, of the α-N C(sp^3)–H bond in the amine-based alkylating agents (**3**–**7**, **13**, **14**) forming iminium-borohydride ion pairs **16** (Scheme 6b, step (i)). Analogous ion pairs have been observed by Santini and co-workers using NMR spectroscopy (cf. Scheme 1A).[14] The electrophilic iminium **16** is trapped with an indole **1** (or oxindole **8**), forging a new C–C bond (step (ii)) in an analogous fashion to the Mannich reaction. Proton transfers enable the ion pair **17** to eliminate the amine **18** (which can be recovered from the reaction) via an $E1_{CB}$-type mechanism (step (iii)).[40] The α,β-unsaturated iminium-based ion pair **19** is reduced by the borohydride counterion, producing the alkylated indoles **2** (and oxindoles **9**) and regenerating the borane-catalyst (step (iv)). In the boron-catalyzed alkylation/ring opening cascade process (cf. Scheme 5), the cyclic nature of the iminium **20** enables the amino fragment to be retained in product **15** after elimination (Scheme 6c).

In summary, we have developed a new approach to the direct C3 alkylation of indoles and oxindoles. Using a $B(C_6F_5)_3$ catalyst and amine-derived alkylating agents, we exploit the underexplored ability of boranes to cleave heterolytically α-N C(sp^3)–H bonds in a catalytic C–C bond-forming reaction. This method provides a metal-free and complementary approach to the few existing methods for the direct C3 alkylation of indoles. Unlike other procedures, this $B(C_6F_5)_3$-catalyzed methodology encompasses several classes of indole, including 1-, 2-, and 1,2-substituted indoles, and allows previously unreported direct methylations. The reaction displays broad scope and exceptional chemoselectivity, avoiding *N*-methylation and formation of 3,3′-bisindolylmethanes in indole substrates, and dialkylation in oxindoles. Other alkylations are also reported, including a novel alkylation-ring opening cascade process to generate privileged 4-(3-indolyl)butylamines from *N*-aryl pyrrolidines.

■ ASSOCIATED CONTENT

Supporting Information

Information about the data that underpins the results presented in this article, including how to access them, can be found in the Cardiff University data catalogue at http://doi.org/10.17035/d.2020.0104936560 or from the lead authors upon request. The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c01141.

Experimental procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

https://dx.doi.org/10.1021/acscatal.0c01141
ACS Catal. 2020, 10, 4835–4840

■ ACKNOWLEDGMENTS

S.B., R.L.M., and L.C.M. gratefully acknowledge the School of Chemistry, Cardiff University for generous support and the Leverhulme Trust for a Research Project Grant (No. RPG-2015-361). R.L.M. would like to acknowledge the EPSRC for a research fellowship (No. EP/R026912/1). A.A.-M., L.W., and A.P.P. thank the School of Chemistry, University of Leicester, for their generous support and the Royal Society for a Research Grant (No. RGS\R1\191082).

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(30) The amine byproduct (cf. amine **18**, Scheme 6) was recovered in 98% yield.

(31) Benzylating agent **4b** was marginally better over the analogous alkylating agent based on amine **6**.

(32) Benzofurans, furans, benzothiophenes, and thiophenes were unreactive, and pyrroles gave low yields. See the Supporting Information for details.

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(35) In the case of oxindoles **9a**, yields were improved upon removal of the $O(SiEt_3)_2$ byproduct by simply applying a vacuum. See the Supporting Information.

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(37) Wasa has previously shown that *N*-aryl pyrrolidines undergo hydride abstraction; see ref 19.

(38) Electron-rich aromatic rings can be removed from nitrogen under oxidative conditions (cf. PMP protecting groups). For a relevant example, see ref 19b.

(39) Partial deuterium incorporation at the *N*-CH_3 site of **2a**-d_3 may indicate that hydride abstraction may also occur at *N*-CH_3, or that a 1,5-prototropic shift in intermediate **19** (R = CH_3) occurs prior to hydride transfer (cf. Scheme 6b, step iv).

(40) Attempts to prevent the elimination and isolate the corresponding aminomethylation derivative of **17** were unsuccessful. For a related elimination-reduction sequence, see: Deb, M. L.; Baruah, P. K. Deamination of Indole Mannich Bases: An Efficient Route to 3-Benzyl/Alkylindoles via a Metal-Free Transfer Hydrogenation Under Microwave Irradiation. *COCAT* **2015**, *3*, 84−89.

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